Improvements in Clinical Measures With ANX005: Interim Phase 2 Results of ANX005 in Patients With Huntington's Disease

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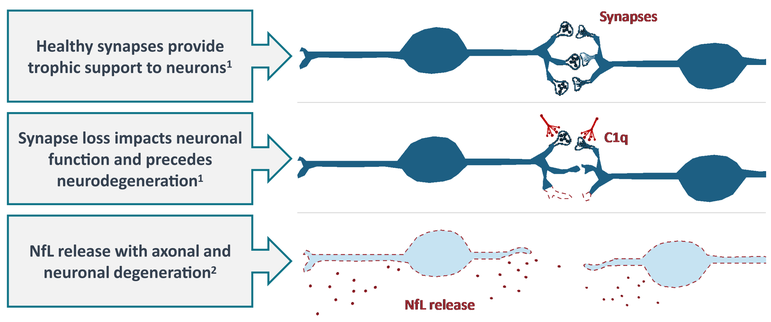
Introduction

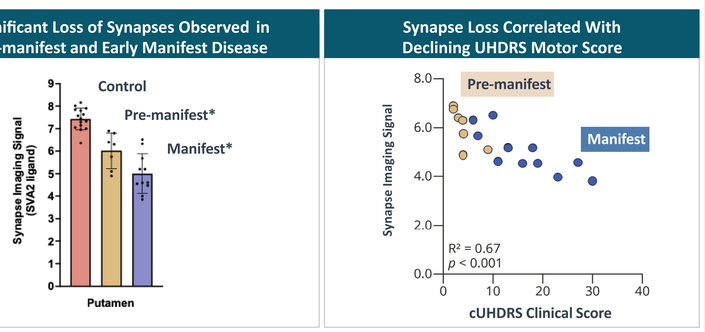
- Increased complement pathway activity driving synaptic loss and disability has been observed in patients with Huntington's disease (HD), a fatal, neurodegenerative disease

Synapse Loss Impacts Neuronal Function and Precedes Neuronal Loss and NfL Release



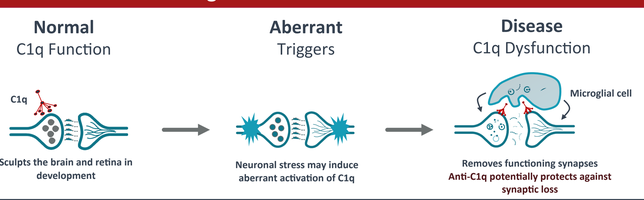
NfL, neurofilament.

Synapse Loss Is Associated With Progressive Functional Decline in Early HD Patients, Preceding Loss of Neurons[3,4]



Graphs modified from Delva A, et al. *Neurology*. 2022;98:e83-e94.
*Significant versus control.
UHDRS, Unified Huntington's Disease Rating Scale.

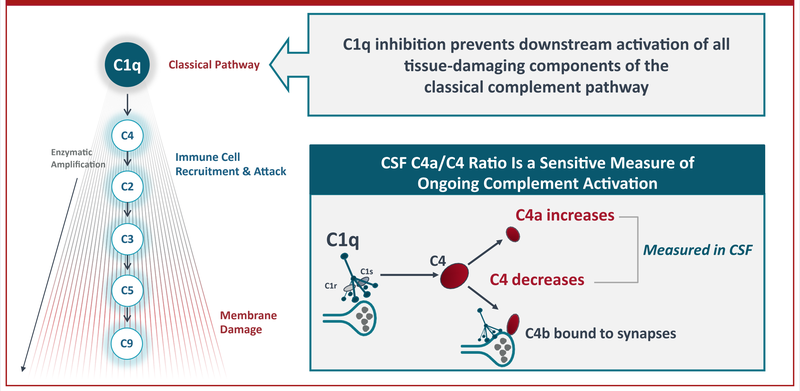
Inhibiting Aberrant Classical Complement Activity Protects Synapses, Improves Neuronal Function & Blocks Degeneration



- In **neurodegenerative diseases**, C1q and downstream classical complement components drive immune cell attack on synapses
- **Synapse loss** causes functional decline, neuroinflammation, and neuronal loss
- C1q blockade can protect synapses, neurons, and neuronal function in several disease models, including Huntington's disease

- Complement expression and activation are elevated in many neurodegenerative diseases, including HD[5]
  - Cerebral spinal fluid (CSF) C4a levels are elevated in patients with HD and increase with disease progression
  - Excess CSF C4a levels in patients with HD is associated with functional decline and disease severity

Excessive Complement Activity Is Observed in Patients with HD



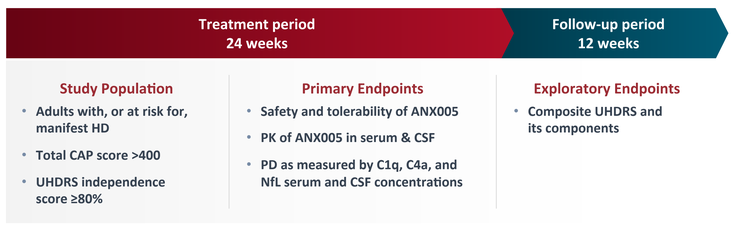
- As the initiating molecule of the classical complement cascade, C1q is an attractive target for preventing complement activation and its multiple tissue-damaging effects
  - Inhibition of C1q blocks initiation of the classical complement cascade
  - Blocking C1q prevents activation of all downstream components of the classical pathway that drive a localized immune response and tissue destruction
- By selectively targeting C1q and only blocking the classical complement pathway, the alternative and lectin pathways are left intact, which is potentially important for maintaining pathogen surveillance

ANX005 Was Designed to Inhibit C1q, the Initiating Molecule of the Classical Complement Cascade

- ANX005 is a humanized monoclonal antibody targeting C1q that was designed to completely inhibit the classical complement pathway

Interim Results From HD-01 (NCT04514367): A Phase 2, Multicenter, Open-Label Trial of ANX005 in Patients With, or at Risk for, Early Manifest HD

Study Design



CAP, CAG-age product; NfL,neurofilament; PD, pharmacodynamic; PK, pharmacokinetics; UHDRS, Unified Huntington's Disease Rating Scale.

Results

- For this interim analysis, 28 patients who had received at least one dose of ANX005 were included (**Table 1**)

Table 1. Baseline demographics

Characteristics	HD-01
Age, mean (SD), years	49.7 (12.5)
Female, %	42.9
CAG repeat length, mean (SD)	44.6 (3.5)
CAP score, mean (SD)	505.7 (57.9)
Manifest HD, n (%)	25 (89.3)
CSF C4a, mean (SD), ng/mL	13.9 (8.2)
Baseline plasma NfL, mean (SD), pg/mL	NA
Baseline CSF NfL, mean (SD), pg/mL	NA
cUHDRS, mean (SD)	**10.4 (3.2)**
Total functional capacity , mean (SD)	10.6 (2.2)
Total motor score, mean (SD)	21.6 (12.6)
Symbol digit modalities test, mean (SD)	29.7 (11.3)
Stroop word reading test, mean (SD)	59.0 (18.7)

CAP, CAG-age product; CSF, cerebrospinal fluid; cUHDRS, composite Unified Huntington's Disease Scale; HD, Huntington's Disease; NA, not applicable; NfL, neurofilament.

- Interim data show that treatment with ANX005 resulted in full target engagement of C1q in both serum and CSF

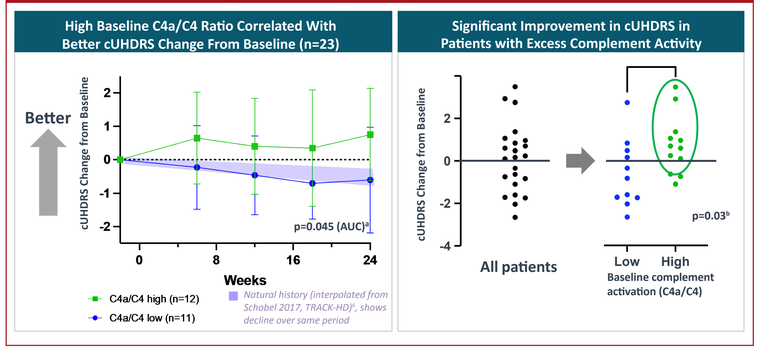
Summary of Safety

- Overall, ANX005 was generally well-tolerated through 6 months of dosing
  - Majority of adverse events (AEs) occurred during initial day 1 infusion (~92.9%); the majority were low grade
- There were 5 patients who discontinued ANX005 treatment
  - 2 non-drug related reasons (COVID, withdrew consent)
  - 3 drug-related AEs, including 2 serious AEs and 1 drug-related AE of special interest (reversible hemolysis with minimal anemia)
- There were 2 serious AEs
  - Symptoms and signs of lupus (mucocutaneous), which resolved post drug cessation
  - Idiopathic pneumonitis stabilized post dosing cessation (follow-up ongoing)
- No deaths and no serious infections occurred

Preliminary Analysis of Efficacy Using Unified Huntington's Disease Rating Scale

- Preliminary efficacy analysis was conducted for 23 patients after excluding 3 early terminations and 2 serious AEs
- Baseline C4a/C4 was measured to evaluate the hypothesis of excess complement activation as a predictor of ANX005 response
- Patients were divided into two groups

Clinical Improvement Was Statistically Better in Patients With High Baseline C4a/C4 Complement Activation



[a]Comparing high vs low C4a/C4 groups.
[b]Exploratory analysis showed statistical significance p=0.03.

HD-01 Phase 2 Study Observations

- **Interim results from HD-01 showed that ANX005 was generally well-tolerated through 6 months of dosing**
  - **Clinical function maintained in overall cohort at 6 months on key UHDRS and composite UHDRS scores**
  - **Statistically differentiated response in patients with excess baseline complement activity**
  - **NfL levels remained consistent and comparable to natural history data**
  - **Use of C4a biomarker appeared to help identify patients with higher complement activation levels at baseline and differentiated clinical response to ANX005**
- **Data provide opportunity for continued development of ANX005 for the treatment of HD**

References

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Acknowledgments

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Disclosures

AM, BH, RA, TY, SK: Employee, Annexon Biosciences; Equity, Annexon Biosciences.

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